Remarks

Based on the amendments to the claims and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Status of the Claims

Claims 1-3, 6-17, 20-24, 27-37, 73-77, 79-82, 106-109, 112, 140, 143-174, are pending in this application. Claims 1, 15, 22, 106, 157, 158, and 161 are independent claims. Claims 79-82, 106-109, 112, 143-153, and 155-156 have been withdrawn from consideration.

Support for the amendments to claims 9 and 10 can be found in originally filed claims 9 and 10. Support for amended claim 168 can be found throughout the specification, *inter alia,* at page 29, line 10 to page 36, line 20.

II. Summary of the Office Action

In the Office Action dated July 30, 2002, the Examiner made 2 rejections of the claims. Applicants respectfully offer the following remarks to overcome these rejections.

III. The Rejection of Claims 9-14, 27-29, 31, 33-34, 76, 157, 159-160, and 168-174 Under 35 U.S.C. § 112, second paragraph Must Be Withdrawn

In the Office Action at section 3, pages 3 and 4, claims 9-14, 27-29, 31, 33-34, 76, 157, 159-160, and 168-174 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner alleges that claims 9-14, 27-29, 31, and 168-174 are indefinite in that they 1) fail to employ proper Markush type language; and 2) include members of the Markush group in parentheses. Although Applicants believe that the claim language is clear and that it distinctly points out and claims the present invention, in the interests of speeding the prosecution of this application, claims 9, 10 and 168 have been amended to adopt the suggested Markush language and to remove the parentheses. With regard to the remaining claims, 11-14, 27-29, 31, and 170-174, Applicants believe the claims as written employ proper Markush language where appropriate and do not contain members of the Markush group in parentheses. The term in parentheses in claims 15 and 27 (HEPES) is the common acronym used for the buffer "N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulfonic acid]" that immediately precedes the term in parentheses. Should the Examiner consider that this term creates confusion, Applicants will amend the claims to remove the term. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner alleges that claims 33 and 34 are indefinite in that they recite "293 embryonic kidney cell." Applicants respectfully submit that "293 cells" are a well known and commercially available cell line derived from human embryonic kidney cells. The Examiner is invited to contact the American Type Culture Collection (ATCC) at http://www.atcc.org/SearchCatalogs/longview.cfm?view=ce,881833,CRL-1573&text=293 for a detailed description of the cell line. With regard to use of the phrase "or a derivative thereof," Applicants respectfully submit that a derivative of a cell line would be readily understood by those skilled in the art to be any cell or cell line

derived from a given cell line by any means, thus, the phrase "or a derivative thereof" does not render the claims indefinite. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

The Examiner alleges that claims 157 and 159-160 are indefinite in that they recite "a method for replacing protein" as the Examiner asserts that "insulin" and "transferrin" are more clearly defined as growth hormones. Applicants respectfully submit that the claims are clear and definite as written. Proteins come in many species, for example, receptors, transport proteins, enzymes, some types of hormones, etc. While a protein, for example, insulin might also be classified as a hormone, nevertheless, insulin, a poly-amino acid molecule, is still a protein. Thus, the recitation of "protein" in no way renders the claims indefinite. In pertinent part, the MPEP states:

> In reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph. See, e.g., *Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 ((Fed. Cir. 2000).

MPEP 2173.02.

Applicants respectfully submit that one skilled in the art could readily determine the scope of the claimed invention upon reading the present claims and, therefore, the claims are in compliance with 35 U.S.C. §112, second paragraph. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

IV. The Rejection of Claims 1-3, 6-17, 20-24, 27-37, 73-77, 140, 154, and 157-174 Under 35 U.S.C. § 103(a) as Obvious Over Chessebeuf, et al., Shuler, et al., and Parenteau, et al. Must Be Withdrawn

In the Office Action, at section 4, pages 4 and 5, claims 1-3, 6-17, 20-24, 27-37, 73-77, 140, 154, and 157-174 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Chessebeuf, *et al.* (reference A on the PTO form 892 accompanying the Office Action, hereinafter "Chessebeuf") in view of Shuler, *et al.* (reference B on the PTO form 892 accompanying the Office Action, hereinafter "Shuler") and Parenteau, *et al.* (reference C on the PTO form 892 accompanying the Office Action, hereinafter "Parenteau"). Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 1, 15, 22, 157, 158, and 161 are independent claims. Claim 1 is drawn to a method of cultivating a mammalian cell in suspension *in vitro* by obtaining a mammalian cell to be cultivated in suspension and contacting said cell with a serum-free, chemically defined cell culture medium comprising at least one polyanionic or polycationic compound, wherein said medium supports the cultivation of said cell in suspension, with the proviso that the medium does not contain dextran sulfate. Claims 2, 3, 7-14, and 140 depend—directly or indirectly—from claim 1.

Claim 15 is drawn to a method of cultivating a mammalian cell in suspension *in vitro* comprising obtaining a mammalian cell to be cultivated in suspension and contacting said cell with a chemically defined cell culture medium comprising a specifically recited set of ingredients wherein each ingredient is present in an amount which supports the cultivation of said cell in suspension, with the proviso that the medium does not contain dextran sulfate. Claims 16, 17, 20, 21, and 154 depend—directly or indirectly—from claim 15.

Claim 22 is drawn to a method of cultivating a mammalian cell in suspension *in vitro* by obtaining a mammalian cell to be cultivated in suspension and contacting said cell with a serum-free, chemically defined cell culture medium obtained by combining a basal medium with at least one polyanionic or polycationic compound, wherein said medium supports the cultivation of said cell in suspension, with the proviso that the medium does not contain dextran sulfate.

Claims 23, 24, and 27-29 depend—directly or indirectly—from claim 22.

Claims 30-37 and 73-77 depend—directly or indirectly—from any one of claims 1, 15, or 22. Claim 157 is drawn to a method for replacing protein in a mammalian cell culture medium, said method comprising replacing insulin with a Zn^{2+} salt and replacing transferrin with a Fe^{2+} chelate and/or a Fe^{3+} chelate. Claims 159 and 160 depend—directly or indirectly—from claim 157.

Claim 158 is drawn to a method of cultivating a mammalian cell in suspension *in vitro* by obtaining a mammalian cell to be cultivated in suspension and contacting said cell with a serum-free, non-animal derived cell culture medium comprising at least one polyanionic or polycationic compound, wherein said medium supports the cultivation of said cell in suspension, with the proviso that the medium does not contain dextran sulfate.

Claim 161 is drawn to a method of cultivating 293 cells in suspension *in vitro* by obtaining 293 cells to be cultivated in suspension and contacting the cells with a serum-free, chemically defined cell culture medium, wherein the medium supports the cultivation of the cell in suspension. Claims 162-174 depend—directly or indirectly—on claim 161.

In pertinent part, the MPEP states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP § 2143.

Further, when the teachings of a prior art reference are considered:

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied* 469 U.S. 851 (1984)

MPEP §2141.02

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention for at least 2 reasons: 1) especially with regard to claims to culturing mammalian cells in suspension in media containing a polyanionic or polycationic compound, one skilled in the art would have had no motivation to combine the cited references when the teachings of the references were considered in their entirety; and 2) especially with regard to claims to methods of replacing protein in a medium and claims to a method of culturing 293 cells in suspension, the cited references do not teach all the limitations of the claims.

The Examiner cites Chessebeuf as teaching serum free mammalian cell culture and methods for culturing cells in a defined medium. Shuler is cited as teaching suspension culture methods and media therefor. The Examiner notes that Shuler discloses the use of polysulfated polyanions for insect cell culture and that dextran sulfate can produce problems for suspension culture of animal or mammalian cells. The

Examiner asserts that Parenteau teaches chemically defined cell culture media and methods for culturing mammalian cells and media containing ethanolamine, and all of the ingredients of amino acids, salts, vitamins, hormones, etc.

The Examiner then concludes:

> It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to replace the dextran as disclosed by Chessebeuf with heparin or some other related and like compound to culture mammal cells as disclosed by Shuler et al. Further, to employ a chemically define culture medium is clearly within the skill of the art as the same is disclosed by Parentaeau [sic] et al. One of skill would have expected successful results for culturing all of the ingredients disclosed by the secondary reference in a culture medium similar to Chessebeuf et al. since Shuler clearly teaches that there can be problems with dextran sulfate when culturing animal/mammalian cells. The specific ingredients, cell numbers, culture medium, etc. of the specific methods and compositions therefore, are clearly taught, or at least, suggested by the cited combination of prior art. One of skill would have been motivated to exclude dextran sulfate as well. Shuler clearly provides the motivation for one skill to exclude dextran sulfate. Therefore, the claims are prima facie obvious over the newly applied art.

Office Action, page 5.

Chessebeuf discloses the culture of animal cells in a serum-free medium supplemented with fatty acids and lipophile biopolymer. Chessebeuf, column 2, lines 17-26. The cells of Chessebeuf are attached to the culture vessels. See, for example, Chessebeuf column 5, lines 19-40, column 7, lines 8-10, and the Examples. Chessebeuf does not disclose or suggest the *suspension* culture of mammalian cells (*e.g.*, 293 cells) as called for in claims 1, 15, 22, 158, and 161 and claims dependent thereon. The lipophilic polymer of Chessebeuf is not a polyanionic or polycationic compound as called for in claims 1, 15, 22, and 158 (see column 3, lines 65-68), nor does Chessebeuf suggest such a polyanionic or polycationic compound. Chessebeuf does not disclose or suggest

the replacement of protein in media as called for in claim 157 and claims dependent thereon. Thus, Chessebeuf is seriously deficient as a reference against the present claims.

The Examiner attempts to cure the deficiencies of Chessebeuf by citing Shuler and Parenteau. Shuler discloses the use of polysulfated polyanions for the suspension cell culture of an *insect* cell line, TN5B1-4. Shuler, column 5, lines 14-17. Shuler specifically notes that these compounds cause aggregation of mammalian cells. Shuler, column 12, lines 1-12. Shuler does not disclose or suggest the suspension culture of mammalian cells nor does Shuler disclose or suggest replacing protein in the cell culture medium. Parenteau discloses the culture of attached cells (column 5, lines 61-67) in a medium comprising insulin or an insulin-like growth factor (column 5, lines 21-23). Parenteau does not disclose or suggest suspension culture of cells nor the replacement of protein in a medium.

With regard to claims to methods of suspension culture of mammalian cells in media comprising polyanionic or polycationic compounds, the two references disclosing culturing of mammalian cells, Chessebeuf and Parenteau, do so in attached cultures and do not disclose or suggest suspension culture and do not disclose or suggest the addition of polyanionic or polycationic compounds. Shuler discloses suspension culture of insect cells using polysulfated polyanions but specifically teaches that these compounds result in aggregation of mammalian cells. Thus, Shuler clearly teaches away from the use of his identified compounds in mammalian cell culture. One of skill in the art would have had no motivation to include the polysulfated polyanions of Shuler in mammalian cell culture in view of the explicit teaching that the result of including such compounds in a mammalian cell culture would be aggregation of the cells. Thus, the combination of

references is improper, at least in part, because the teachings of Shuler were not considered in their entirety.

With regard to claims to the suspension culture of 293 cells, none of the cited references teach or suggest the culture of 293 cells. Thus, the cited references do not teach or suggest all the limitations of these claims.

With regard to claims to a method of replacing protein in a mammalian cell culture medium, none of the cited references teach or suggest the replacement of protein in a cell culture medium. In fact, Parenteau specifically discloses media containing insulin or insulin-like growth factors. Parenteau, column 5, lines 21-22. Chessebeuf discloses that it may be necessary to supplement media with hormones or growth factors. Chessebeuf, column 4, lines 33-42. Chessebeuf does not disclose or suggest making the replacements called for in the present claims. Thus, none of the cited references disclose or suggest the presently claimed replacements and, therefore, the cited references do not teach or suggest all the limitations of these claims.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the

outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

9. (Amended) The method of claim 1, wherein said medium further comprises one or more ingredients selected from the group[of ingredients] consisting of one or more amino acids, one or more vitamins, one or more inorganic salts, one or more buffering salts, one or more sugars, one or more lipids, transferrin, [(or]transferrin substitutes[)], [and]insulin, [(or]and insulin substitutes[)].

10. (Amended) The method of claim 9, wherein said medium further comprises one or more supplements selected from the group [of supplements] consisting of one or more cytokines, heparin, one or more animal peptides, one or more yeast peptides and one or more plant peptides.

168. (Amended) The method of claim 162, wherein the medium further comprises one or more ingredients selected from the group[of ingredients] consisting of one or more amino acids, one or more vitamins, one or more inorganic salts, one or more buffering salts, one or more sugars, one or more lipids, transferrin, one or more transferrin substitutes, insulin, and one or more insulin substitutes.